



Influence of solvent and substituents on the reaction of *N*-alkylthioacetamides with dimethyl acetylenedicarboxylate: synthesis of functionalized thiophenes containing an exocyclic double bond

Konstantin L. Obydenov^{a,*}, Elena L. Klimareva^a, Marya F. Kosterina^a, Pavel A. Slepukhin^b, Yury Yu. Morzherin^a

^a Ural Federal University, Mira 19, Ekaterinburg 620002, Russia

^b I. Postovsky Institute of Organic Synthesis, Kovalevskoy 22, Ekaterinburg 620090, Russia

ARTICLE INFO

Article history:

Received 30 April 2013

Revised 16 June 2013

Accepted 26 June 2013

Available online 3 July 2013

Keywords:

Acetylenedicarboxylate

Thioacetamide

Thiophene

Thiazole

Exocyclic double bond

ABSTRACT

The reaction of thioacetamides with dimethyl acetylenedicarboxylate affords 3-oxothien-2-ylidene or 4-oxothiazol-2,5-ylidene derivatives based on the structure of the thioacetamides and the solvent employed. The structural features of the 3-oxothien-2-ylidenes are discussed.

© 2013 The Authors. Published by Elsevier Ltd. Open access under [CC BY-NC-ND license](#).

Thiophenes containing double bonds attract attention as photochromic molecular switches¹ and as models of D- π -A (donor-spacer-acceptor) systems.² There are a number of methods in the literature for the preparation of thiophenes containing exocyclic double bonds (Scheme 1). In general, these compounds are synthesized from isothiocyanates (pathway A)^{3,4} or by the oxidation of thiophenes (pathway B).^{5–7}

In this Letter, we report a method for the preparation of the thiophenes containing exocyclic double bonds by reaction of *N*-monosubstituted thioacetamides with dimethyl acetylenedicarboxylate (DMAD) (pathway C). In reactions of *N,N*-disubstituted thioacetamides with DMAD the formation of thiazoles does not occur, as was reported previously by us.⁸ Although there are a number of possible pathways for the reaction between acetylenedicarboxylates and *N*-substituted thioamides,^{9–11} formation of thiophenes is now reported.

In the present work we report that reactions between cyanothioacetamides **1a–d** and DMAD **2** proceed via different pathways depending on the structure of **1** and the solvent. To establish the influence of the solvent, heterocyclization reactions were conducted in ethanol or acetic acid (Scheme 2).

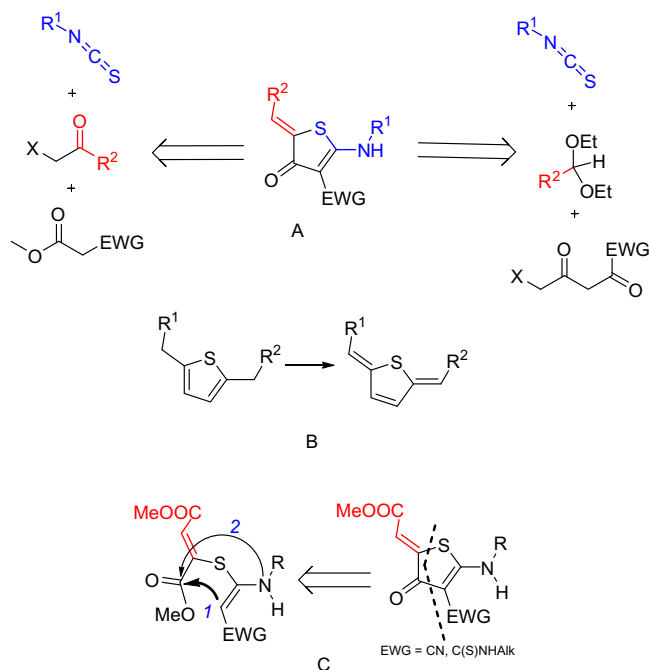
Thiophenes **5c,d** were formed as the major products from cyanothioacetamides with bulky substituents on nitrogen **1c,d**.^{12–14} However, in the case of the cyanothioacetamides **1c,d** it was shown that the main products were (2-cyanomethylen-4-oxothiazolidin-5-ylidene)acetic acid methyl esters **4c,d** when the reaction was conducted in ethanol (Table 1). The thiazoles **4** and thiophenes **5** were easily separated by recrystallization from acetic acid. With cyanothioacetamides **1a,b** the formation of thiophene derivatives was not observed.^{15,16}

The percentage increase in the formation of the thiophenes can be due to the formation of iminium intermediate **3** when acetic was used as the solvent.

At the same time *N,N*-dialkylmalonodithioamides **6a–d** react with DMAD to afford only 3-oxothien-2(3*H*)-ylidene derivatives **8a–d** (Scheme 3) in 40–65% yields.^{17–19} This result is additional to earlier work when the reaction was carried out in acetone and only the formation of thiazoles was observed.¹¹ Malonothioacetamides **6a–d** are more reactive in comparison with cyanothioacetamides **1a–d**, therefore the reaction proceeds even at room temperature.

* Corresponding author. Tel./fax: +7 8 (343) 375 48 18.

E-mail address: k.l.obydenov@ustu.ru (K.L. Obydenov).



Scheme 1. General pathways toward thiophenes containing exocyclic double bonds.

Table 1
Synthesis of thiazoles **4** and thiophenes **5**

R	Solvent ^a	Product ratio 4:5 ^b	Yield ^c (%)
(a) Me	EtOH	1:0	50
	CH ₃ COOH	1:0	51
(b) Bn	EtOH	1:0	62
	CH ₃ COOH	1:0	56
(c) Cy	EtOH	4:1 ^d	37
	CH ₃ COOH	2:3	75
(d) i-Pr	EtOH	2:1 ^d	57
	CH ₃ COOH	1:3	53

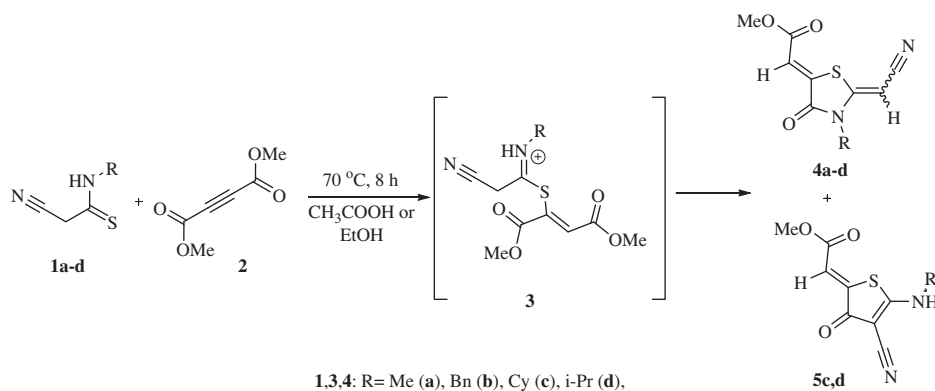
^a All reactions were carried out using equimolar amounts of each compound in 10 ml of solvent, 70 °C, 8 h.

^b Ratio of the thiazole **4** and thiophene **5**.

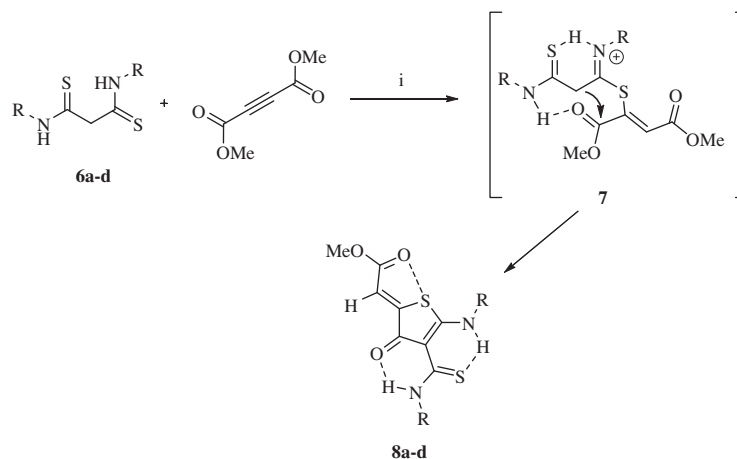
^c Isolated yield of the thiazoles **4** and thiophenes **5**.

^d Ratio determined from the ¹H NMR spectrum of the crude product.

It is worth noting that the second thioamide group was unaffected even when 2 equiv of DMAD were used. Presumably the reaction route is governed by formation of iminium derivative **7** as a result of intermolecular hydrogen bond formation thanks to the presence of the second thioamide group (see [Scheme 3](#)). According to X-ray crystal data²⁰ the thiophene **8a** has a planar structure which is stabilized by two intramolecular hydrogen bonds (N₂–H₂···S₂ and N₁–H₁···O₂), and three weak interactions exist due to the presence of nearby located heteroatoms: O₃ and



Scheme 2. Synthesis of thiazoles **4** and thiophenes **5**.



Scheme 3. Reagents and conditions: (i) CH₃COOH or EtOH + 1 equiv CH₃COOH, rt, 40 °C, 4 h.

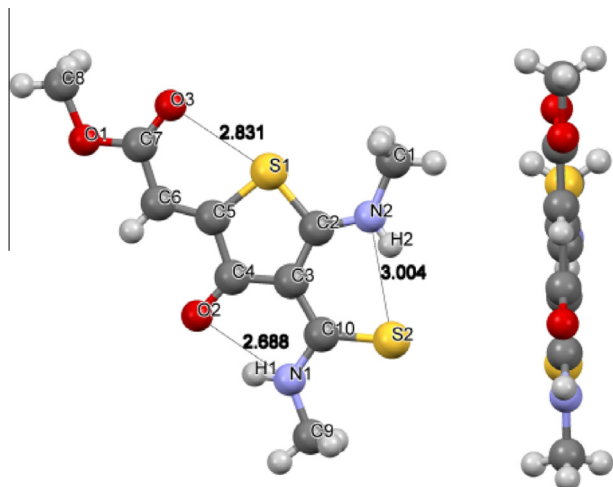
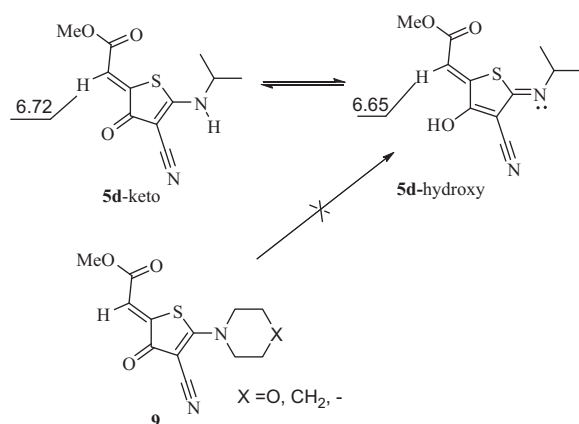


Figure 1. Molecular structure and selected geometric parameters (Å) of compound **8a**.



Scheme 4. The equilibrium of thiophene **5b** in solution.

S₁, N₂ and S₂, O₂ and N₁ (see Fig. 1). In all probability, intramolecular hydrogen bonds exist in intermediate **7** that similarly facilitate the direction of further condensation.

The thiophenes **8a–d** have groups which can undergo further heterocyclizations to form bicyclic heterocyclic system.

In the ¹H NMR spectra of thiazoles **4a–d** and thiophenes **5c,d**, we observed doubling of the signals of all groups, including the signals assigned to the exocyclic double bond hydrogen atoms (5–7 ppm), which indicates that isomers were formed, unlike with thiophenes **8a–d**. The tautomeric equilibrium of (2-methylen-4-oxo-thiazolidin-5-ylidene)acetic acid ethers has been described previously.²⁵ In the earlier work, tautomerism of (Z)-methyl 2-[4-cyano-5-(dialkylamino)-3-oxothien-2(3H)-ylidene]acetic acids esters **9** was not observed.⁸ We propose that isomerization of thiophenes **5c,d** could occur via tautomerism (Scheme 4).

An additional ¹H NMR experiment in which the spectra of thiophene **5d** were recorded over a temperature range from rt to 100 °C (Fig. 2) was done. In the ¹H NMR spectra of compound **5b** recorded in DMSO-*d*₆ at 80 °C and 100 °C the doubling of the signals disappeared, while in the spectra **8c** recorded in CDCl₃, doubling of the signals was not observed, even on cooling to –60 °C. Hence, isomerization is via tautomerism and not the formation of regioisomers during cyanothioacetamides heterocyclization with DMAD.

In summary, we have developed a novel pathway for N-substituted thioacetamide heterocyclization with DMAD. Several

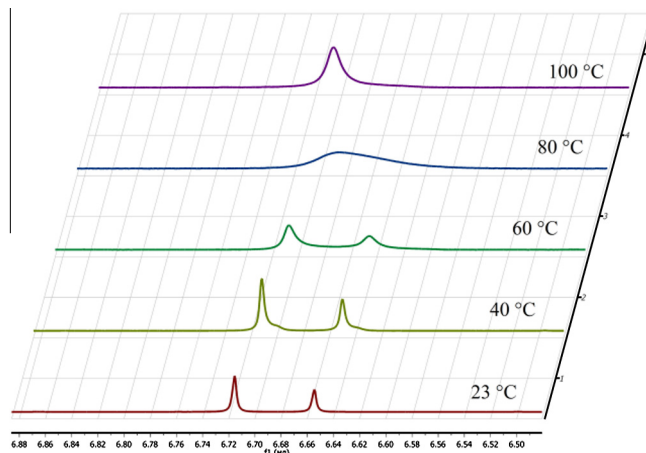


Figure 2. Spectra of the exocyclic double bond hydrogen atom in thiophene **5d** at different temperatures.

novel 3-oxo-3H-thien-2-ylidenes were prepared. It was shown that formation of 3-oxo-3H-thien-2-ylidenes in acetic acid was favored due to the hindered substituent at nitrogen and the presence of a second thioamide group. The thioamide group leads to a planar stable structure of 2-[4-(methylcarbamothioyl)-3-oxothien-2(3H)-ylidene]acetate. It was revealed that 2-[2-(cyanomethylene)-4-oxothiazolidin-5-ylidene]acetates exist in a solution together with the hydroxy forms as a result of tautomerism.

Acknowledgments

The research was carried out in terms of Ural Federal University development program with the financial support of young scientist.

References and notes

- Bren, V. A.; Dubonosov, A. D.; Minkin, V. I.; Tsukanov, A. V.; Gribanova, T. N.; Shepelenko, E. N.; Revinsky, Y. V.; Rybalkin, V. P. *J. Phys. Org. Chem.* **2007**, *20*, 917–928.
- Manzhos, S.; Segawa, H.; Yamashita, K. *Chem. Phys. Lett.* **2012**, *527*, 51–56.
- Knies, A.; Gruner, M.; Mayer, R. *Monatsh. Chem.* **1996**, *127*, 1173–1187.
- Khmel'nitskaya, E. Yu.; Grigor'ev, N. B.; Ryabova, S. Yu.; Trofimkin, Yu. I.; Azimov, V. A.; Granik, V. G. *Chem. Heterocycl. Compd.* **2002**, *38*, 1357–1362.
- Takekuma, S.-I.; Sonoda, K.; Minematsu, T.; Takekuma, H. *Tetrahedron* **2008**, *64*, 3802–3812.
- Marin, L.; Van Mierloo, S.; Zhang, Y.; Robeyns, K.; Champagne, B.; Adriaenssens, P.; Lutsen, L.; Vanderzande, D.; Maes, W. *Tetrahedron* **2013**, *69*, 2260.
- Bromby, A. D.; Jansonius, R. P.; Sutherland, T. C. *J. Org. Chem.* **2013**, *78*, 1612–1620.
- Kosterina, M. F.; Morzherin, Yu. Yu.; Tkachev, A. V.; Rybalova, T. V.; Gatilov, Yu. V.; Bakulev, V. A. *Russ. Chem. Bull.* **2002**, *51*, 653.
- Danilina, N. A.; Mikhailov, L. E.; Ivin, B. A. *Russ. J. Org. Chem.* **2006**, *42*, 783–814.
- Britsun, V. N.; Esipenko, A. N.; Lozinskii, M. O. *Chem. Heterocycl. Compd.* **2008**, *44*, 1429–1459.
- Obydenov, K. L.; Kosterina, M. F.; Klimareva, E. L.; Bakulev, V. A.; Morzherin, Yu. Yu. *Russ. Chem. Bull.* **2011**, *5*, 1016–1018.
- General procedure.* To a suspension of cyanthioacetamide (1.2 mmol) in 20 ml of glacial AcOH was added (0.095 ml, DMAD, 1.2 mmol) at 40 °C. The mixture was stirred at 70 °C for 8 h. The resulting precipitate was filtered to give the pure solid product. Thiazole derivatives were obtained by dilution of the filtrate with water, filtration, and recrystallization from ethanol if necessary.
- (Z)-Methyl 2-[4-cyano-5-(isopropylamino)-3-oxothien-2(3H)-ylidene]acetate (**5d**). Yield 34%, yellow crystals; mp 270–271 °C. ¹H NMR (400 MHz, DMSO-*d*₆, 25 °C): (the keto-form (61%)) 1.32 (s, 6H, CH₃), 3.79 (s, 3H, CH₃), 3.89–3.97 (m, 1H, CH), 6.72 (s, 1H, =CH), 10.43 (s, 1H, NH); hydroxy-form (39%) 1.30 (s, 6H, CH₃), 3.78 (s, 3H, CH₃), 4.40–4.48 (m, 1H, CH), 6.65 (s, 1H, =CH), 10.28 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-*d*₆, 25 °C): (mixture of isomers) 21.91, 22.31, 48.52, 50.99, 52.58, 77.00, 78.10, 114.04, 114.11, 115.26, 115.49, 144.42, 145.30, 165.87, 166.05, 170.66, 173.90, 180.77, 182.81. Anal. calcd for C₁₁H₁₂N₂O₃S: C, 52.37; H, 4.79; N, 11.10; S, 12.71; found: C, 52.10; H, 4.70; N, 11.15; S, 12.85. MS (EI, 70 eV), *m/z* (%): 252 [M]⁺ (83).
- (Z)-Methyl 2-[(Z)-2-(cyanomethylene)-3-cyclohexyl-4-oxothiazolidin-5-ylidene]acetate (**5c**). Yield 30%, pale yellow powder; mp 259–261 °C. ¹H NMR

- (400 MHz, DMSO- d_6 , 25 °C): 1.36–1.19 (3H, m, CHCy), 1.80–1.59 (5H, m, CHCy), 2.14–2.10 (2H, m, CHCy), 3.78 (3H, s, OCH₃), 4.09 (1H, m, CHCy), 6.04 (1H, s, CH), 6.74 (1H, s, =CH). ¹³C NMR (100 MHz, DMSO- d_6 , 25 °C): 24.97, 25.70, 27.99, 115.06, 53.09, 56.89, 74.28, 117.25, 140.63, 154.87, 164.23, 166.60. Anal. calcd for C₁₄H₁₆N₂O₃S: C, 57.52; H, 5.52; N, 9.58; S, 10.97; found: C, 57.55; H, 5.50; N, 9.60; S, 10.92. MS (EI, 70 eV), *m/z* (%): 292 [M]⁺ (60).
15. *General procedure.* To a suspension of *N*-substituted cyanothioacetamide (1.1 mmol) in 20 ml of glacial AcOH was added (0.160 ml, DMAD, 1.1 mmol) at room temperature. The mixture was stirred at temperature 70 °C for 8 h, then diluted with ice-cold water (20 ml), stirred for 30 min, and filtered. The precipitate was dried over P₂O₅ under reduced pressure.
16. (*Z*)-Methyl 2-(2-(cyanomethylene)-3-benzyl-4-oxothiazolidin-5-ylidene)acetate (**4b**). Yield: 0.2 g (63%); mp 119–120 °C, pale yellow powder. ¹H NMR (400 MHz, DMSO- d_6 , 25 °C): 3.82 (s, 3H, OCH₃), 5.00 (s, 2H, CH₂), 5.82 (s, 1H, CH), 6.90 (s, 1H, CH), 7.38–7.29 (m, 5H, Ar-H); Anal. calcd for C₁₅H₁₂N₂O₃S: C, 60.02; H, 4.02; N, 9.33; S, 10.58; found: C, 59.99; H, 4.03; N, 9.33; S, 10.68. MS (EI, 70 eV), *m/z* (%): 300 [M]⁺ (8.9).
17. *General procedure.* To a suspension of malonothioamide (1.2 mmol) in 20 ml of glacial AcOH was added (0.095 ml, DMAD, 1.2 mmol) at 40 °C. The mixture was stirred at 40 °C for 4 h. In the cases of thiophenes **4a,b**, filtration gave compound as yellow fibers after washing with AcOH (10 ml) and then of distilled water (50 ml). The precipitate was dried over P₂O₅ under reduced pressure. In the cases of thiophenes **4c,d**, the mixture was diluted with of ice-cold water (20 ml) then mixture was stirred for 30 min and filtered. The precipitate was recrystallized from ethanol, filtered, washed with ethanol 1 ml, and dried over P₂O₅ under reduced pressure.
18. (*Z*)-Benzyl 2-[5-(benzylamino)-4-(methylcarbamothioyl)-3-oxothien-2(3H)-ylidene]acetate (**8b**). Yield: 0.18 g (65%), yellow fibrous precipitate; mp 148–149 °C. ¹H NMR (400 MHz, CDCl₃, 25 °C): 3.85 (s, 3H, CH₃), 4.81 (d, 2H, *J* = 6.4, CH₂), 4.89 (d, 2H, *J* = 5.2, CH₂), 3.82 (s, 3H, CH₃), 6.94 (s, 1H, =CH), 7.29–7.43 (m, 10H, 2Ph), 11.83 (s, 1H, NH); 13.68 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO- d_6 , 25 °C): 46.30, 49.57, 52.01, 101.36, 115.85, 126.88, 127.08, 127.27, 127.59, 128.09, 128.43, 135.01, 136.64, 143.19, 165.40, 177.24 (S=C), 181.36 (COOMe), 184.99 (C=O). Anal. calcd for C₂₂H₂₀N₂O₃S₂: C, 66.24; H, 4.75; N, 6.60; S, 15.11; found: C, 66.25; H, 4.80; N, 6.60; S, 15.10. MS (EI, 70 eV), *m/z* (%): 424 [M]⁺ (33).
19. (*Z*)-Methyl 2-[5-(isopropylamino)-4-(isopropylcarbamothioyl)-3-oxothien-2(3H)-ylidene]acetate (**8d**). Yield: 0.2 g (65%), yellow crystals; mp 140–142 °C. ¹H NMR (400 MHz, CDCl₃, 25 °C): 1.31 (d, *J* = 6.4 Hz, 6H, CH₃), 1.46 (d, *J* = 6.4 Hz, 6H, CH₃), 3.86 (s, 3H, OCH₃), 3.92–4.04 (m, 1H, CH), 4.62–4.73 (m, 1H, CH), 6.92 (s, 1H, =CH), 11.52 (s, 1H, NH), 13.52 (s, 1H, NH). ¹³C NMR (100 MHz, CDCl₃, 25 °C): δ 21.58, 22.97, 44.88, 50.43, 52.53, 101.41, 115.95, 114.93, 166.92, 176.33, 182.31, 184.12. Anal. calcd for C₁₄H₂₀N₂O₃S₂: C, 51.19; H, 6.14; N, 8.53; S, 19.53; found: C, 51.20; H, 6.10; N, 8.50; S, 19.55. MS (EI, 70 eV), *m/z* (%): 328 [M]⁺ (30).
20. The structure of compound **7a** was deposited with the Cambridge Crystallographic Data Centre (No. CCDC 930944; deposited@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk/data_request/cif).
21. Guo, Y.; Yan, Y.; Zhi, X.; Yang, C.; Hu, H. *Bioorg. Med. Chem. Lett.* **2013**, 3382–3384.
22. Mérou, J.-Y.; Chichereau, L.; Desarbres, E.; Gadonneix, P. *Synthesis* **1996**, 519–524.
23. Palacios, F.; Alonso, C.; Rubiales, G.; Villegas, M. *Tetrahedron* **2009**, 1119–1124.
24. Palluotto, F.; Campagna, F.; Carotti, A.; Ferappi, M.; Rosato, A.; Vitali, C. *II Farmaco* **2002**, 63–69.
25. Berseneva, V. S.; Tkachev, A. V.; Morzherin, Yu. Yu.; Dehaen, W.; Luyten, I.; Toppet, S.; Bakulev, V. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2133–2136.